Effect of Concomitant Antiseizure Medications on the Safety and Efficacy of Ganaxolone for the Treatment of Seizures Associated with CDKL5 Deficiency Disorder: Findings From the Phase 3 Marigold Study

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BACKGROUND

- Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is a developmental and epileptic encephalopathy characterized by global developmental impairment and early-onset, refractory seizures[1]
- Ganaxolone, a neuroactive steroid and positive allosteric modulator that acts on both synaptic and extrasynaptic $GABA_A$ receptors, was shown to significantly reduce seizures associated with CDD[2,3]
- In the multinational, placebo-controlled, double-blind Marigold Study (NCT03572933), major motor seizure frequency (MMSF) was reduced with ganaxolone treatment over 17 weeks by a Hodges-Lehmann difference of 27.1% over placebo[3]

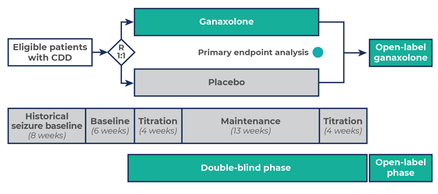
OBJECTIVE

- Post hoc evaluation of the safety and efficacy of ganaxolone in subgroups of patients who were taking the most frequently used concomitant daily antiseizure medications (ASMs) and concomitant rescue medications during the 17-week double-blind phase of Marigold

METHODS

- Study design
  - A total of 101 patients with CDD aged 2-19 years were enrolled and randomized
  - Eligible patients were permitted to take up to 4 concomitant ASMs during the study
- Key eligibility criteria
  - Pathogenic or likely pathogenic *CDKL5* variant
  - ≥16 major motor seizures (defined as bilateral tonic, generalized tonic-clonic, atonic/drop, bilateral clonic, or focal to bilateral tonic-clonic) per month during the historical seizure baseline
- Ganaxolone dosing
  - 3 times/day with food at a maintenance dose of up to 63 mg/kg/day or 1800 mg/day

Figure 1. Design of the Marigold Study



CDKLS, cyclin-dependent kinase-like 5; CDD, CDKLS deficiency disorder; R, randomization.

- Endpoints
  - Post hoc analyses of safety and efficacy were conducted in subgroups of patients taking each of the four most frequently used ASMs (valproate, levetiracetam, clobazam, and vigabatrin)
  - Efficacy was assessed by the placebo-adjusted percent reduction in MMSF during the 17-week treatment period relative to the 6-week baseline
  - Comparative efficacy of placebo and ganaxolone treatment groups in relation to a concomitant ASM was analyzed using cumulative response curves
  - An efficacy analysis evaluating the correlation of rescue medication use and percent changes in MMSF was also conducted
  - Safety outcomes included treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)

RESULTS

Concomitant Daily Medications

- The concomitant ASMs used by at least 20% of patients from either treatment group during the 17-week double-blind phase were valproate, levetiracetam, clobazam, and vigabatrin (**Table 1**)

Table 1. Concomitant ASM Use by Treatment Group

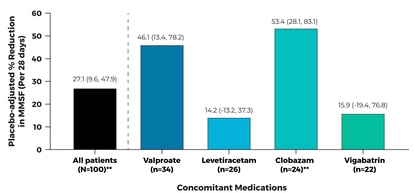
Concomitant ASM	Placebo, n (%) n=51	Ganaxolone, n (%) n=50	Total, n (%) N=101
Valproate	16 (31.4)	18 (36.0)	34 (33.7)
Levetiracetam	13 (25.5)	13 (26.0)	26 (25.7)
Clobazam	13 (25.5)	12 (24.0)	25 (24.8)
Vigabatrin	12 (23.5)	10 (20.0)	22 (21.8)

ASM, antiseizure medication.

Efficacy of Concomitant Daily Medications

- The greatest placebo-adjusted percent reductions in MMSF (Hodges-Lehmann difference) were observed in patients taking clobazam (53.4%) or valproate (46.1%) (**Figure 2**)
- The reduction was 15.9% and 14.2% for patients who were taking vigabatrin and levetiracetam, respectively

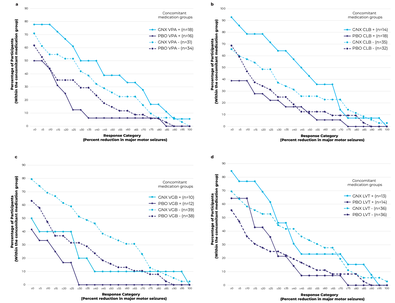
Figure 2. Placebo-Adjusted Percent Reduction of MMSF* by Concomitant Medication Use



*Hodges-Lehmann difference (95% CI) is presented. **One patient did not have baseline seizure data and was excluded from the analysis of seizure reduction.
MMSF, major motor seizure frequency.

Cumulative Response Curves

Figure 3. Cumulative Response Curves of 28-day Seizure Frequency With or Without Concomitant Valproate, Clobazam, Vigabatrin, or Levetiracetam - 13-Week Maintenance Period, Intent-to-Treat Population



CLB, clobazam; GNX, ganaxolone; LVT, levetiracetam; PBO, placebo; VGB, vigabatrin; VPA, valproate.
Intent-to-treat population: all patients who received at least 1 dose of study drug.

- **Valproate:** Not only did ganaxolone-treated patients receiving valproate have greater seizure reductions, but placebo patients receiving valproate achieved substantially smaller reductions (**Figure 3a**)
  - The greater effect size for patients receiving valproate can largely be explained by the placebo response
- **Clobazam:** Placebo responses differed little with or without clobazam (**Figure 3b**). While the overall median difference in response between ganaxolone and placebo was greater in patients receiving clobazam, this difference was not consistent throughout the range of response levels.
- **Vigabatrin:** The overall median difference in MMSF between ganaxolone and placebo was lower in patients taking vigabatrin than in those who did not (**Figure 3c**). However, placebo-treated patients taking vigabatrin had lower reductions in MMSF than those who did not, with no reductions greater than 30%.
  - Therefore, subjects taking vigabatrin fared more poorly regardless of whether they were randomized to the active or placebo arms
  - This strongly suggests that the relatively lower net response for vigabatrin-treated patients was due to underlying patient characteristics rather than a pharmacodynamic interaction between ganaxolone and vigabatrin
- **Levetiracetam:** While the net reduction in major motor seizures for ganaxolone vs placebo was lower than the overall study population (14.2% for patients taking levetiracetam vs 27.1% overall), the cumulative response curves (**Figure 3d**) showed that differences in response based on levetiracetam use varied throughout the range of responses for patients taking either ganaxolone or placebo. At some response levels, the response for patients taking levetiracetam was greater and at others it was less.

Safety of Concomitant Daily Medications

- The prevalence of TEAEs and SAEs were similar in ganaxolone-treated patients across all concomitant ASM subgroups
- The rate of somnolence was higher with ganaxolone treatment than with placebo in concomitant ASM subgroups, consistent with the overall study population (**Table 2**)

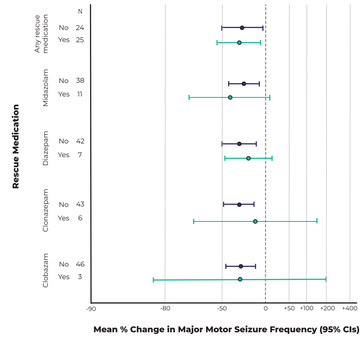
Table 2. Prevalence of Somnolence with Concomitant Medication Use

Group	Placebo, % (n=51)	Ganaxolone, % (n=50)
All Patients	15.7	36.0
Valproate	12.5	55.6
Levetiracetam	15.4	30.8
Clobazam	30.8	33.3
Vigabatrin	8.3	30.0

Rescue Medications

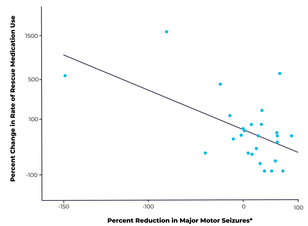
- 25/49 patients in the ganaxolone intent-to-treat population were receiving rescue medication at baseline
  - 17 were using a single rescue medication (midazolam n=7, diazepam n=6, clonazepam n=3, and phenobarbital n=1), 8 were taking 2 or 3 rescue medications, and 24 were taking none
- There were comparable reductions in the percent change in MMSF regardless of the status of rescue medication use or the choice of rescue medication (**Figure 4**)

Figure 4. Mean Percent Reductions in Major Motor Seizures in Ganaxolone-Treated Patients According to Use of the Most Common Rescue Medications



- In evaluating the potential impact of rescue medications on overall seizure reductions, it is important to consider not only whether the patient is taking rescue medications, but also the frequency at which they are used
- An analysis of the relationship of changes in seizure frequency and rescue medication use (**Figure 5**) demonstrated a statistically significant negative correlation between reductions in MMSF and rescue medication use (R=-0.567, *P*=0.003)

Figure 5. Mean 28-day Percent Change in Major Motor Seizure Frequency According to Rescue Medication Use in Ganaxolone-Treated Subjects



*Axis values on log scale.

Conclusions

- **Placebo-adjusted reductions in MMSF were relatively greater for study participants taking concomitant clobazam or valproate**
  - **However, these post hoc comparisons were likely confounded by baseline differences in patient characteristics such as seizure severity or treatment resistance**
- **Safety findings were comparable with different concomitant ASMs**
- **In ganaxolone-treated patients, use of rescue medications decreased with greater improvements in seizure control, indicating that their use was a consequence and not a cause of seizure reductions**
- **Further research could provide insight on the impact of concomitant medications on the efficacy and safety of ganaxolone therapy in patients with CDD**

References

1. Olson HE, et al. *Pediatr Neurol.* 2019;97:18-25.
2. Reddy DS, et al. *Drugs Fut.* 2004;29(3):227-242.
3. Pestana-Knight EM, et al. *Lancet Neurol.* 2022;21(5):417-427.

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